UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,684	02/27/2004	Alan L. Epstein	1920-325N1/09801297	9775

167 7590 08/23/2006

FULBRIGHT AND JAWORSKI LLP
555 S. FLOWER STREET, 41ST FLOOR
LOS ANGELES, CA 90071

EXAMINER	
MERTZ, PREMA MARIA	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,684	EPSTEIN ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *6-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (claims 1-5) in the reply filed on 2/21/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 6-27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

2. It is clear from the declaration that Applicants intend to claim priority to the earlier filed applications. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, in this case the instant application is a continuation of 10/142,120, filed 5/9/2002, now U.S. Pat No. 6,737,064, which is a divisional of 09/443,061, filed 11/18/1999, now U.S. Pat No. 6,403,096, which is a divisional of 08/806,121, filed 12/23/1996, now U.S. Pat No. 6,008,319, specific reference to the earlier filed applications must be made in the instant application as "Cross Reference to Related Applications". This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of non-provisional application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It s suggested that the title be amended to recite "vasopermeability enhancing peptide of human interleukin-2".

Claim Rejections - 35 USC § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 1-5, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth vasoactive peptides consisting of residues 37-58 or 33-58 or 37-72 or 22-58 (SEQ ID NO:1) of amino acid sequence SEQ ID NO:3, substantially free of IL-2 cytokine and therefore the written description is not commensurate in scope with the claims drawn to a vasoactive peptide comprising a fragment of IL-2. Amino acid sequences consisting of residues 37-58 or 33-58 or 37-72 or 22-58 (SEQ ID NO:1) of amino acid sequence SEQ ID NO:3 meet the written description and enablement provisions of 35 U.S.C. 112, first paragraph. However, the indicated claims are directed to encompass homologues of the disclosed amino acid sequences having undisclosed amino acid sequences, which correspond to IL-2 sequences from other species. None of these amino acid sequences meet the written description provision of 35 USC 112, first paragraph.

In the specification on page 10, first full-para, lines 14-27, Applicants disclose that the preferred embodiments of vasoactive peptides are those consisting of residues 37-58 or 33-58 or 37-72 or 22-58 (SEQ ID NO:1) of amino acid sequence SEQ ID NO:3 which is a human IL-2 sequence. *Vas-Cath Inc. v. Makurhar*, 19 USPQ2d 1111, makes clear that applicant must convey with reasonable clarity to those skilled in the art, as the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry whatever is now claimed (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See *Vas-Cath Inc. v. Makurhar*, page 1116).

With the exception of vasoactive peptides consisting of residues 37-58 or 33-58 or 37-72 or 22-58 (SEQ ID NO:1) of amino acid sequence SEQ ID NO:3, the skilled artisan cannot envision the detailed chemical structure of the amino acid sequences encompassed by the instant claims and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a potential method for isolating it, the amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ 2d 1481, 1483. Weighing all factors in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the Applicant was in possession of the claimed invention.

4b. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated vasoactive peptide, said peptide consisting of residues 37-58 or 33-58 or 37-72 or 22-58 (SEQ ID NO:1) of amino acid sequence SEQ ID NO:3, substantially free of IL-2 cytokine activity, does not reasonably provide enablement for "all" vasoactive peptides which are fragments of IL-2 or a peptide consisting essentially of residues 37 to 58 of amino acid sequence SEQ ID NO:1 or a peptide consisting essentially of amino acid sequence SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

PM 8/9/06

With respect to claims 1-5, as recited, what is claimed in the instant invention broadly encompasses "all" vasoactive peptides comprising fragments of IL-2. The specification is non-enabling for the unlimited number of vasoactive peptides comprising a fragment of IL-2 protein, and which are encompassed by the scope of the claims. Claim 1-5 are single means claims (M.P.E.P. 2164.08(a)). In In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), the Courts have held that: "A single means claim, i.e. where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph." (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor). Since no material limitations for the peptide have been recited in the claim and only a biological activity has been recited, the claims encompass every conceivable structure (means) for achieving the stated property (result), a fact situation comparable to Hyatt. The claimed invention encompasses

peptides not envisioned or described in the specification, and neither does the specification disclose how these claimed peptides can be distinguished from each other. The specification only enables peptides of the following amino acid residues 37-58, 33-58, 37-72 and 22-58 of SEQ ID NO:3 as shown in Table I (page 31), the peptides having specific characteristics and properties. These properties may differ structurally, chemically and physically from other known peptides. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which other vasoactive peptides comprising a fragment of IL-2, are encompassed by the scope of the claims is practically infinite and the guidance provided in the specification very little, thereby rendering the results of the assays taught in the specification unpredictable (see pages 30-36). Therefore, it would require undue experimentation to determine which peptides of IL-2 having the desirable biological activity, would be encompassed by the scope of the claims. The disclosure of 4 peptides is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass every and all IL-2 peptides, including mutants thereof. In In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), the Courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are

insufficiently supported and hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Furthermore, the amount of embodiments corresponding to the desirable peptides, may be innumerable, and the enabled embodiments amount to only four. Therefore, there are substantial scientific reasons to doubt the scope of enablement, as set forth above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe any other peptides other than those set forth in Table I, nor does the specification describe any other vasoactive peptides of IL-2, and since it is deemed to constitute undue experimentation to determine all the others, the disclosure is not commensurate with the scope of the claims. Therefore, Applicants are not enabled for peptides having anything less than the amino acid sequence residues 37-58 or 33-58 or 37-72 or 22-58 of SEQ ID NO:3. It is suggested that by employing conventional claim language, the preamble to claim 1 read approximately as follows: "An isolated and purified vasoactive peptide, selected from the group consisting of residues 37 to 58 of SEQ ID NO:3...." as supported by the instant specification.

Claim 1 also recites "fragment of IL-2..", which limitation is non-enabled by the specification in the absence of reference to a subset of amino acid sequences comprising the domains to which the functional properties of the peptides have been ascribed. While the specification discloses that the vasoactive peptides of the instant invention are directed to permeability enhancing peptides that satisfy the need for potent vasoactive agents which improve the uptake of therapeutic and diagnostic agents at a tumor site (see page 6, lines 11-15), it provides no guidance as to which amino acids might comprise the minimum residues of a fragment of IL-2 which retains any enabled functional property peculiar to the instant peptides. One would not have a reasonable expectation of successfully making a representative number of amino acid fragments having the desirable biological activity consistent with the scope of the claims. Additionally, one would reasonably expect that fragmentation of the 133 amino acid residue IL-2 polypeptide would abolish activity because activity is determined not only by primary sequence, but also by three-dimensional structure, as, for example, is the case for the ligand binding site of a receptor or for a catalytic site of an enzyme. Any arbitrary fragment of the amino acid sequence of SEQ ID NO:3 would not be expected to confer the desirable activity. Therefore, in the absence of delimiting amino acid sequences that make up the functional domains of the instant IL-2 protein, a person of ordinary skill in the art would be unable to make fragments of the amino acid sequence of IL-2 embraced by the claims without undue experimentation to determine which fragments have the desirable biological activity.

Claim 1 also recites "capable of...". The specification is non-enabling for vasoactive peptides that do not enhance vascular permeability or form a dimer (claim 5) and are only capable of, if further modified such that they can then enhance vascular permeability or form a

dimer, because applicants have not taught how to further modify the peptides such that they can enhance vascular permeability. It has been held that an element is "capable of" performing a function is not a positive limitation but only requires the ability to perform. It does not constitute a limitation in any patentable sense. In re Hutchison, 69 USPQ 138.

With respect to claims 3-4, the specification does not enable peptides consisting "essentially of" an amino acid sequence. The specification does not enable the skilled artisan to make and/or use peptides that have essentially the same amino acid sequence as the ones disclosed (residues 37 to 58 of SEQ ID NO:3 or SEQ ID NO:1). The issue here is how substantial must the sequence identity be, and what portions constitute this identity? The specification does not teach which residues can be conservatively substituted without affecting the functional activity of the peptide. It is known to the skilled artisan that conservative amino acid substitutions outside of the active site of a protein will not affect the functional activity of the protein; however, amino acid substitutions, even conservative alterations, within the active site can inactivate the protein or change its functional activity. Absent the specific degree of sequence identity, it is unpredictable if the peptide would also possess the same activity. Thus, without guidance as to which residues can be conservatively substituted, the skilled artisan would not be able to make and/or use peptides consisting essentially of residues 37 to 58 of SEQ ID NO:3 or consisting essentially of amino acid sequence SEQ ID NO:1.

Claim rejections-35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5a. Claims 1-5, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as vague and indefinite for several reasons.

Claim 1, lines 2-3, recites "substantially free of cytokine activity". It is unclear which cytokine activity is referred to in the claim.

Claim 1 is vague and indefinite because it recites "fragment of IL-2" and it is unclear which species of IL-2 is being referred to in the claim. It is suggested that the claim be amended to recite human IL-2.

Claims 3-4 are rejected as vague and indefinite for reciting "essentially of" the same amino acid residues because this phrase encompasses any peptide with an amino acid sequence 51% identical to residues 37 to 58 of SEQ ID NO:3 or 51% identical to SEQ ID NO:1. Therefore, the metes and bounds of the claims are unclear.

Claim 3, line 2, is vague and indefinite because it is unclear whether residues 37 to 58 are part of SEQ D NO:1 or are SEQ ID NO:1. Appropriate correction is requested.

Similarly, claim 4 is confusing because it is unclear if the amino acid sequence being claimed is set forth in SEQ ID NO:1.

Claim 5, line 2 is vague and indefinite because the phrase "includes at least" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 2 is rejected as vague and indefinite insofar as it depends on claim 1 for its limitations.

Claim rejections-Double Patenting

Non-statutory double patenting rejection (obviousness-type)

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6a. Claims 1-5, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6, 008,319.

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-5, in the instant application claim a vasoactive peptide which is a fragment of IL-2. Claims 1-5 of U.S. Patent No. 6, 008, 319 (having the same two inventors as the instant application), claims a vasoactive peptide comprising a fragment of IL-2 containing amino acids 37-58 of SEQ ID NO:3. It is clear that the claims in the instant application and in the patent differ in scope. Therefore, the instant claims are generic to claims 1-5 in the patent and encompasses subject matter to which allowed claims in the patent is a species. The patented claims are obvious from the instant claims because the patented claims are directed to a specific embodiment encompassed by the instant claims. The patented products are included in the instant claims.

The patented claims if infringed upon would also result in infringement of the broad claims of the instant application. Allowance of the pending claim, therefore, would have the effect of extending the enforceable life of the allowed claims beyond the statutory limit.

Conclusion

No claim is allowed.

Claims 1-5 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz

Prema Mertz Ph.D., J.D.
Primary Examiner
Art Unit 1646
August 9, 2006